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Eisai Co., Ltd.

EISAI RECEIVES POSITIVE CHMP OPINION ON NEW INDICATION FOR ANTICANCER AGENT LENVATINIB IN COMBINATION WITH EVEROLIMUS FOR TREATMENT OF ADVANCED RENAL CELL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its European regional headquarters Eisai Europe Ltd. (Location: U.K.) has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on anticancer agent lenvatinib mesylate (generic name, "lenvatinib") in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF) targeted therapy. If approved, lenvatinib will be launched under the brand name Kisplyx® for this indication.

The CHMP's positive opinion was based on a Phase II clinical study (Study 205)[1] that evaluated the safety and efficacy of lenvatinib in combination with everolimus in patients with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy. From the results of the study, the group who received the combination of lenvatinib plus everolimus demonstrated a significant extension in progression free survival, the study's primary endpoint, as well as a higher objective response rate compared to the everolimus alone group. The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher were diarrhea, hypertension and fatigue.

The number of patients with renal cancer in Europe is estimated to be 115,000,[2] and renal cell carcinoma comprises more than 90% of all malignancies of the kidney.[3] For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment method is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

Currently lenvatinib has been launched in countries including the United States, Japan and in Europe under the product name Lenvima® as a treatment for refractory thyroid cancer. Furthermore, in May 2016, lenvatinib was approved in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy by the U.S. Food and Drug Administration in the United States.

Eisai positions oncology as a key therapeutic area, and is aiming to discovery revolutionary new medicines with the potential to cure cancer. Eisai remains committed to providing further clinical evidence for lenvatinib aimed at maximizing value of the drug as it seeks to contribute further to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families, and healthcare providers.

*Please refer to the following notes for the approved indications in the United States, Japan and Europe

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[Notes to editors]

1. About lenvatinib mesylate (generic name, "lenvatinib")

Discovered and developed in-house, lenvatinib is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFRα; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained approval for lenvatinib as a treatment for refractory thyroid cancer in over 40 countries including in the United States, Japan, in Europe, Korea, Canada, and Mexico, and is undergoing regulatory review in countries throughout the world including Brazil and South Africa. Specifically, Eisai has obtained approval for the agent indicated in the United States for treatment for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, in Japan for the treatment of unresectable thyroid cancer, and in Europe for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine, respectively.

Furthemore, lenvatinib was also approved in the United States in May 2016 for an additional indication in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy. Meanwhile, Eisai is conducting clinical studies of lenvatinib in several other tumor types such as hepatocellular carcinoma (Phase III), endometrial carcinoma (Phase II), biliary tract cancer (Phase II), and in combination with an immune checkpoint inhibitor (Phase Ib/II).

2. About the Phase II Clinical Study (Study 205)[1]

Study 205 was a multicenter, randomized, open-label study of the combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg), and everolimus alone (10 mg) in patients with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy, and was conducted in Europe and the United States. 153 patients were randomized in a 1:1:1 ratio to one of three treatment arms to compare the efficacy and safety of these three regimens.

From the results of the study, the combination of lenvatinib plus everolimus group demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group (median PFS for the lenvatinib plus everolimus group: 14.6 months vs median PFS for the everolimus alone group: 5.5 months; Hazard Ratio (HR) 0.40 [95% CI: 0.24-0.68], p=0.0005). Additionally, median PFS for the lenvatinib alone group was 7.4 months, demonstrating an extension in PFS compared to the everolimus alone group (HR: 0.61 [95% CI: 0.38-0.98]).

The study also assessed objective response rate (ORR) and overall survival (OS) as secondary endpoints. Regarding ORR, both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in ORR compared to the everolimus alone group (lenvatinib plus everolimus: 43%, lenvatinib alone: 27%, everolimus alone: 6%). Furthermore, regarding OS, an updated analysis carried out in December 2014 suggested that lenvatinib plus everolimus extends OS compared to everolimus alone (HR 0.51 [95% CI=0.30-0.88]).

The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher (Common Terminology Criteria for Adverse Events) were diarrhea, hypertension and fatigue.

3. About Renal Cell Carcinoma

The number of patients with renal cancer was estimated to be approximately 338,000 worldwide, including approximately 115,000 in Europe, 58,000 in the United States and 17,000 in Japan.[2] Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,[3] and occurs when malignant cells are found in the lining of the tubules of the kidney. The incidence of renal cell carcinoma in people aged in their late 50s is rising, and is more likely to affect men than women. For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment method is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

1 Motzer, R, et al. "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial." *The Lancet Oncology*, 2015; 16, 1473-1482.

2 Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, http://globocan.iarc.fr/

3 Eble J.N, ed. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. 3rd ed. *World Health Organization Classification of Tumours*, vol.7 (IARC, 2004)